Disease Activity Influences Cardiovascular Risk Reclassification Based on Carotid Ultrasound in Patients with Psoriatic Arthritis

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ABSTRACT. ***Objective.*** Because the addition of carotid ultrasound (US) into composite cardiovascular (CV) risk scores has been found effective for identifying patients with inflammatory arthritis and high CV risk, we aimed to determine whether its use would facilitate the reclassification of patients with psoriatic arthritis (PsA) into the very high Systematic Coronary Risk Evaluation (SCORE) risk category and whether this might be related to disease features.

Methods. This was a cross-sectional study involving 206 patients who fulfilled ClASsification for Psoriatic ARthritis criteria for PsA, and 179 controls. We assessed lipid profile, SCORE, disease activity measurements, and the presence of carotid plaques and carotid intima-media thickness by ultrasonography. A multivariable regression analysis, adjusted for classic CV risk factors, was performed to evaluate whether the risk of reclassification could be explained by disease-related features and to assess the most parsimonious combination of risk reclassification predictors.

Results. Forty-seven percent of patients were reclassified into a very high SCORE risk category after carotid US compared to 26% of controls ($p < 0.001$). Patients included in the low SCORE risk category were those who were more commonly reclassified (30% vs 14%, $p = 0.002$). The Disease Activity Index for PsA (DAPSA) score was associated with reclassification (β 1.10, 95% CI 1.02–1.19; $p = 0.019$) after adjusting for age and traditional CV risk factors. A model containing SCORE plus age, statin use, and DAPSA score yielded the highest discriminatory accuracy compared to the SCORE-alone model (area under the receiver-operating characteristic curve 0.863, 95% CI 0.789–0.936 vs 0.716, 95% CI 0.668–0.764; $p < 0.001$).

Conclusion. Patients with PsA are more frequently reclassified into the very high SCORE risk category following carotid US assessment than controls. This was independently explained by the disease activity. (First Release June 15 2020; J Rheumatol 2020;47:1344–53; doi:10.3899/jrheum.190729)

Key Indexing Terms:
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There is growing evidence that psoriatic arthritis (PsA) patients have a higher cardiovascular (CV) disease burden than the general population[1]. Exposure to an increased inflammation load is associated with a higher prevalence of atherosclerosis in these individuals[2]. Previous studies have reported that this occurred independently of traditional CV risk factors and correlated with PsA disease duration and increased inflammatory markers[3,4]. Moreover, patients with PsA lacking traditional CV risk factors were found to have the more commonly observed subclinical atherosclerosis, manifested by a higher frequency of endothelial dysfunction, greater carotid intima-media wall thickness (cIMT), and a higher frequency of carotid plaques than healthy controls[5,6]. Additionally, increased cIMT independently correlated with variables of disease activity and conventional risk factors of atherosclerosis in patients with PsA[7]. This is of great relevance, because the presence of carotid atherosclerosis was associated with an increased risk of experiencing future CV events in patients with PsA[8].

Prediction score algorithms for CV disease (CVD), such as the Framingham Risk Score and the Systematic Coronary Risk Evaluation (SCORE), were reported to be of limited value in correctly identifying high CV risk patients with PsA[7,9]. This implies that such risk charts do not correctly identify patients who might benefit from intensive management of CV risk factors. For this reason, the search for noninvasive tools that would facilitate the identification of patients with PsA who are at very high CV risk is of great relevance. In this regard, the reclassification of individuals included in the moderate or low categories, based on the SCORE, into the very high CV risk category using carotid ultrasound (US) has been reported in patients with systemic lupus erythematosus (SLE)[10] and rheumatoid arthritis[11,12].

According to the 2016 European Guidelines on CVD Prevention in Clinical Practice[13], carotid artery plaque assessment using US has gained support as a way of reclassifying those patients for whom the SCORE is thought to underestimate the actual CV risk. However, there are still limited data available to define a candidate profile for this evaluation, the cost-effectiveness of which would be greater. Taking this into account, we aimed to determine whether the use of carotid US would facilitate the reclassification of patients with PsA into the very high CV risk SCORE category and whether this could be related to characteristics assessed in the daily clinical practice, particularly those related to disease features.

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MATERIALS AND METHODS

Study participants. This was a cross-sectional study that included 206 patients with PsA and 179 controls. All of them were 18 years old or older, had a clinical diagnosis of PsA, and were enrolled based upon the international ClASsification for Psoriatic ARthritis (CASPAR) study[14]. They had been diagnosed by rheumatologists and were periodically followed up at rheumatology outpatient clinics. For the purpose of inclusion in the present study, PsA disease duration had to be ≥ 1 year. Although longterm anti–tumor necrosis factor (TNF)-α therapy has been found to reduce aortic stiffness and cIMT progression in patients with PsA[15,16], those undergoing anti–TNF-α, interleukin 17 inhibitors, or other biological therapies were not excluded from the present study. Likewise, because glucocorticoids are often used in the management of PsA, patients taking prednisone were not excluded. The controls (n = 179) were community-based, recruited by general practitioners in primary health centers of the Cantabria region. Controls with family history of any inflammatory or autoimmune rheumatic diseases were excluded. None of the patients and controls had established CVD. Diabetes mellitus patients were included when target organ damage was not present. The study protocol was approved by the Institutional Review Committee at Hospital Marqués de Valdecilla in Santander, Spain, and all subjects provided informed written consent (approval number: 2016.052).

Assessments and data collection. Surveys in patients with PsA and controls were performed to assess CV risk factors and medication. Hypertension was defined as a systolic or a diastolic blood pressure > 140 and 90 mmHg, respectively. Dyslipidemia was defined if 1 of the following factors was present: total cholesterol > 200 mg/dl, triglycerides > 150 mg/dl, high-density lipoprotein cholesterol < 40 mg/dl in men or < 50 mg/dl in women, or low-density lipoprotein (LDL) cholesterol > 130 mg/dl. At the time of assessment, all patients were evaluated using 2 clinical measures of disease activity: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[17] and the Disease Activity Index for PsA (DAPSA)[18]. In addition, a functional status index (Bath Ankylosing Spondylitis Functional Index)[19], a patient life effect measure (PsA Impact of Disease Score)[20], 2 cutaneous indices (Psoriasis Area and Severity Index score and Psoriasis Global Assessment)[21], and the Nail Psoriasis Severity Index were used[22]. Further, high-sensitivity C-reactive protein (CRP) was assessed, and standard techniques were used to measure serum lipids.

Carotid US assessment. Carotid US was performed to determine cIMT in the common carotid artery and to detect focal plaques in the extracranial carotid tree both in patients with PsA and in controls[12,23]. A commercially available scanner, Mylab 70 (Esaote) equipped with a 7–12 MHz linear transducer and an automated software-guided radiofrequency technique — Quality Intima Media Thickness in real-time (QIMT, Esaote) — was used for this purpose. Based on the Mannheim consensus, plaque criteria in the accessible extracranial carotid tree (common carotid artery, bulb, and internal carotid artery) were defined as follows: a focal protrusion in the lumen measuring at least cIMT > 1.5 mm, a protrusion at least 50% greater than the surrounding cIMT, or an arterial lumen encroaching > 0.5 mm[24].

Statistical analysis. Patients and controls with carotid plaques based on US assessment were reclassified into very high SCORE risk category. Subjects without plaques were maintained in their original SCORE category. cIMT was not used to determine reclassification because according to current guidelines[13], cIMT is not considered an unequivocal CVD on imaging. Univariate differences between reclassified and non-reclassified patients were assessed through Student t, Mann-Whitney U, chi-square, or Fisher's exact tests according to normal distribution or the number of subjects. Logistic regression analysis adjusted for the variables with a p value < 0.20

in the univariate analysis was performed to assess the relationship between PsA disease-related data and the presence of reclassification. An all-sets logistic regression model was constructed to describe the most parsimonious combination of risk reclassification predictors according to Akaike Information Criteria, Schwarz Bayesian Criterion, area under the curve, and Hosmer-Lemeshow goodness-of-fit statistics. For characteristics associated with reclassification and that were included in the predictive model, sensitivity versus false positive frequency (1-specificity) was analyzed using receiver-operating characteristic curves (ROC). To determine the optimal cutoff value of baseline characteristics in predicting reclassification, we calculated the Youden index using the following formula: sensitivity + specificity – 1, with the maximum obtained value corresponding to the optimal cutoff point. To estimate the increase in prediction accuracy between models, we used logistic regression to calculate the ROC curves and the area under the ROC curves (AUC). The SCORE AUC was thus considered the reference and was compared to the other model when adding PsA-related data (age, statin use, and DAPSA score). A comparison of ROC curves to test the statistical significance of the difference between the areas under 2 dependent ROC curves (derived from the same cases) was conducted using the method of DeLong, *et al*[25]. Reclassification differences between models were studied through the net reclassification index (NRI) and integrated discrimination improvement (IDI) as previously described[26]. Similarly, calibration of the models was calculated using the Hosmer-Lemeshow goodness-of-fit test by grouping individuals on the basis of deciles[27,28]. All the analyses used a 5% two-sided significance level and were performed using SPSS software, version 24 (IBM Corp.). A p value < 0.05 was considered statistically significant.

RESULTS

Demographic, laboratory, and disease-related data. A total of 206 patients with PsA and 179 sex-matched controls with a mean ± SD age of 45 ± 8 and 41 ± 9 years, respectively, were included in this study. Demographic and disease-related characteristics of the participants are shown in Table 1. Body mass index (26.9 ± 5.8 vs 25.4 ± 4.2; p = 0.010) and waist circumference (94 ± 15 vs 91 ± 15 cm, p = 0.048) were higher in patients with PsA than controls. Differences between patients and controls in the prevalence of traditional CV risk factors were also observed. In this regard, patients were more commonly hypertensive (37% vs 12%, $p < 0.001$), smokers (28% vs 18%, p = 0.017), and diabetic (10% vs 2%, p = 0.002). A lipid profile assessment revealed lower levels of total cholesterol (0.006) and LDL cholesterol (0.023) in patients compared to controls. The median PsA disease duration was 4.6 years [interquartile range (IQR) 2.0–10.9]. Psoriasis was present in 73% of patients at the time of the study and 10% were positive for HLA-B27. An extended version of Table 1 is available as Supplementary Table 1 (available with the online version of this article).

Regarding carotid US assessment, 49% of the patients with PsA had carotid plaques compared to 26% of controls ($p < 0.001$). The average cIMT in patients and controls was 0.679 ± 0.165 mm and 0.606 ± 0.116 mm, respectively ($p < 0.001$).

SCORE risk category reclassification after carotid sonography. Following SCORE risk chart stratification, 101 (49%) patients and 139 (78%) controls were included in the low CV risk category. In contrast, none of the controls and only 8 (4%) patients fulfilled the definition for very high CV risk when the risk charts were applied (Table 2). Interestingly, carotid US assessments revealed a significantly higher frequency of reclassification in patients with PsA compared to controls (47% vs 26%, $p < 0.001$). In this regard, 30 of the 101 patients (30%) and 19 of the 139 controls (14%) who fulfilled the definition for low CV risk, according to the SCORE risk charts, had carotid plaques; consequently, they were reclassified into the very high risk category (30% vs 14%, p = 0.002). Fifty-four of 78 patients (69%) and 18 of 28 controls (64%; p = 0.54) included in the moderate-risk SCORE category had carotid plaques and consequently were also reclassified into the very high CV risk category. Similarly, 12 of 19 patients with PsA (63%) and 10 of 12 controls (83%) included in the high CV risk SCORE category prior to carotid US assessment were reclassified into the very high risk category once that test was performed (p = 0.42; Table 2).

Similar results were obtained when analyses were performed separating patients according to whether they had current anti–TNF-α therapy. Both groups disclosed a higher probability of being reclassified compared to controls (Supplementary Table 2, available with the online version of this article).

Differences between reclassified and non-reclassified patients into very high CV risk categories after carotid US assessment. Several differences were observed in the recorded characteristics of patients with PsA who were reclassified following the carotid US assessment and those who were not reclassified (Table 3). Reclassified patients were older (57 ± 9 yrs vs 50 ± 13 yrs, $p < 0.001$), and more commonly had hypertension (54% vs 22%, $p < 0.001$) and obesity (28% vs 14%, p = 0.011).

As expected, patients with PsA who were reclassified following a carotid US had greater cIMT than those who were not reclassified (0.725 ± 157 mm vs 0.638 ± 0.162 mm, $p < 0.001$). Interestingly, neither laboratory variables related to the lipid profile nor CRP values revealed any differences between reclassified and non-reclassified patients with the exception of total cholesterol (197 ± 36 mg/dl vs 179 ± 40 mg/dl, p = 0.001) and LDL cholesterol (116 ± 35 mg/dl vs 106 ± 34 mg/dl, p = 0.032), which were lower in reclassified patients.

Regarding PsA-related features, some differences were also observed between these 2 groups of patients. Those with peripheral polyarthritis were more commonly reclassified following a carotid US assessment than the other patients. In addition, disease duration was found to be higher in the reclassified patients [5.7 (IQR 2.2–12.5) vs 4.1 (IQR 1.4–8.0) yrs, p = 0.023]. However, this association was lost after adjusting for age and traditional CV risk factors. The DAPSA score, both as a continuous [6.10 (0.05–15.10) vs 1.92 (0.00–10.01), p = 0.056] and categorical measure (low, moderate, or high activity vs remission), was found to be higher in reclassified patients in the univariate analysis.

Table 1. Demographic data of 206 psoriatic arthritis (PsA) patients and 179 controls.

	Controls, n = 179	PsA, n = 206	p
Demographics			
Male, n (%)	90 (50)	91 (44)	0.23
Age, yrs	41 ± 9	45 ± 8	**< 0.001**
BMI, kg/m^2	25.4 ± 4.2	26.9 ± 5.8	**0.010**
Waist circumference, cm	91 ± 15	94 ± 15	**0.048**
Systolic pressure, mmHg	121 ± 13	129 ± 18	**< 0.001**
Diastolic pressure, mmHg	76 ± 9	77 ± 11	0.237
Comorbidity, n (%)			
Hypertension	21 (12)	76 (37)	**< 0.001**
Dyslipidemia	106 (59)	114 (55)	0.48
Current smoking	32 (18)	58 (28)	**0.017**
Diabetes	4 (2)	21 (10)	**0.002**
BMI > 30	25 (14)	42 (20)	**0.020**
Laboratory data			
ESR, mm/h	5 (2–9)	6 (3–12)	**0.002**
hsCRP, mg/l	0.8 (0.5–2.0)	0.3 (0.1–0.8)	**0.006**
Cholesterol, mg/dl	199 ± 34	189 ± 30	**0.006**
Triglycerides, mg/dl	103 ± 56	102 ± 52	0.83
LDL-C, mg/dl	119 ± 31	111 ± 34	**0.023**
HDL-C, mg/dl	59 ± 17	57 ± 17	0.27
Atherogenic index	3.62 ± 1.06	3.94 ± 5.89	0.49
PsA-related data			
Type of PsA			
Peripheral oligoarthritis		19 (9)	
Peripheral polyarthritis		124 (60)	
Spondylitis		30 (15)	
Mixed		30 (15)	
Disease duration, yrs		4.6 (2.0–10.9)	
Psoriasis at the time of the study, n (%)		151 (73)	
HLA-B27–positive, n (%)		20 (10)	
Family history of PsA, n (%)		69 (33)	
BASDAI, total score		2.2 (0.0–4.7)	
BASDAI > 4, n (%)		31 (15)	
BASFI, total score		0 (0–3)	
PsAID, total score		1.0 (0.0–2.9)	
DAPSA, total score		4.2 (0.1–13.0)	
BSA, total score		0.75 (0.00–2.05)	
PASI, total score		0.45 (0.00–2.00)	
NAPSI, total score		0.0 (0.0–3.1)	
PGA, total score		0 (0–1)	
Axial symptoms, n (%)		70 (34)	
Peripheral symptoms, n (%)		150 (73)	
Hip symptoms, n (%)		44 (21)	
Enthesitis, n (%)		78 (38)	
Uveitis, n (%)		13 (6)	
Dactylitis, n (%)		51 (25)	
Inflammatory bowel disease, n (%)		14 (7)	
Sacroiliitis on MRI, n (%)		26 (13)	
Syndesmophytes in axial radiograph, n (%)		7 (3)	
Current NSAID, n (%)		162 (79)	
Current prednisone, n (%)		85 (41)	
DMARD, n (%)		154 (75)	
Methotrexate, n (%)		139 (67)	
Anti-TNF therapy, n (%)		87 (42)	
Carotid intima-media assessment			
Carotid plaque, n (%)	47 (26)	100 (49)	**< 0.001**
Bilateral, n (%)	20 (11)	56 (27)	**< 0.001**
cIMT, mm	0.606 ± 0.116	0.679 ± 0.165	**< 0.001**

Data represent mean ± SD or median (IQR) when data were not normally distributed. Data in bold face are statistically significant. BMI: body mass index; ESR: erythrocyte sedimentation rate; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; PsAID: PsA Impact of Disease Score; DAPSA: Disease Activity for Psoriatic Arthritis; BSA: body surface area; PASI: Psoriasis Area and Severity Index; NAPSI: Nail Psoriasis Severity Index; PGA: Psoriasis Global Assessment; MRI: magnetic resonance imaging; NSAID: nonsteroidal antiinflammatory drug; DMARD: disease-modifying antirheumatic drug; TNF: tumor necrosis factor; cIMT: carotid intima-media thickness; IQR: interquartile range.

Table 2. SCORE risk category reclassification after carotid ultrasound assessment.

Initial SCORE risk category		SCORE Risk Category after Carotid Ultrasound Assessment					
		Low	Moderate	High	Very High	Patients Reclassified, %	p*
Controls							
Low	139	120	0	0	19	13.7	
Moderate	28	0	10	0	18	64.3	
High	12	0	0	2	10	83.3	
Very high	0	0	0	0	0	—	
	179	120	10	2	47	26.3	
PsA patients							
Low	101	71	0	0	30	29.7	**0.002**
Moderate	78	0	24	0	54	69.2	0.54
High	19	0	0	7	12	63.2	0.42
Very high	8	0	0	0	8	—	
	206	71	24	7	104	46.6	**< 0.001**

*P values refer to the comparison between patients and controls for each SCORE category and for the total of both populations. Values in bold face are statistically significant. SCORE: Systematic Coronary Risk Evaluation; PsA: psoriatic arthritis.

Moreover, DAPSA score differences were still present when this relationship was constructed after adjusting for confounding factors. Thus DAPSA's positive relationship with reclassification yielded a statistically significant association (β 1.10, 95% CI 1.02–1.19, p = 0.019) after the multivariable analysis. Multivariable regression analysis also confirmed the aforementioned results using DAPSA as a categorical (low, moderate, or high activity vs remission) and ordinal (moderate and high activity, or low activity vs remission) variable. Patients with moderate or high activity, according to their DAPSA score at the time of assessment, exhibited a higher probability of being reclassified compared to the remaining patients (β 15.09, 95% CI 1.69–135.08, p = 0.015). An extended version of Table 3 is available as Supplementary Table 3 (available with the online version of this article).

Predictive model for reclassifying patients into the very high CV risk category following a carotid US assessment. A predictive model was constructed only for those patients with PsA who had been included in the low and moderate risk SCORE categories prior to a carotid US assessment. These variables conjointly represented the most parsimonious model capable of predicting the reclassification of patients with PsA into the very high CV risk category (Table 4): age, use of statins, and DAPSA score. Moreover, an age exceeding 48 years and a DAPSA score ≥ 5 were the cutoffs among the continuous variables that reached the highest Youden indices.

Table 5 represents the discrimination, reclassification, and calibration assessment of the model using clinical data (age, statin use, and DAPSA score) versus the reference SCORE model. The SCORE, which included traditional CV risk factors, showed a statistically significant discrimination of reclassification (AUC 0.716, 95% CI 0.668–0.764). However, the AUC of the model, which contained SCORE plus age, statin use, and the DAPSA score, was found to have higher discrimination (0.863, 95% CI 0.789–0.936, p < 0.001; Figure 1). The addition of clinically related data represented a significant change in NRI versus the SCORE reference model (NRI 0.65, 95% CI 0.38–0.92, p < 0.001). Similarly, IDI was significantly higher in this model compared to that of the SCORE reference (0.46, 95% CI 0.36–0.56, p < 0.001). Model calibration (through a Hosmer-Lemeshow chi-square test) was found to be optimal in the final model (0.89).

DISCUSSION

A carotid US is a noninvasive, well-validated, and reproducible procedure for quantifying the burden of subclinical vascular disease and determining CVD risk. Using this technique, we can measure the cIMT and identify the presence of carotid plaques, which are surrogate markers for atherosclerotic disease. In the present study, we observed not only that use of a carotid US allowed us to reclassify nearly half of the patients with PsA but also that disease activity influenced reclassification, regardless of traditional CV risk factors. In this sense, tools that are commonly used in clinical practice proved useful for identifying patients with PsA who would benefit from a complementary CV assessment.

Reclassification of CV risk using carotid US in PsA has previously been reported. In a recent study of 102 patients[29], 70.6% had intermediate CV risk, 25.5% high CV risk, and 3.9% very high CV risk according to the SCORE risk charts. Of these, 26.5% were upgraded and reclassified into the very high risk category owing to the presence of carotid plaques. However, this study lacked any comparison of reclassification between patients with PsA and healthy individuals. Moreover, the study did not provide information on determinants of this reclassification. In another cross-sectional multicenter descriptive study from the same group, 30.8% of the 176 patients with PsA assessed by SCORE risk charts were subsequently reclassified as having very high risk

Table 3. Differences between reclassified and non-reclassified PsA patients into the very high cardiovascular risk category following carotid ultrasound assessment.

	Reclassification into Very High Risk after Carotid Ultrasound			Adjusted Model*	
	No, n = 109	Yes, n = 97	p	OR (95% CI)	p
cIMT, mm	0.638 ± 0.162	0.725 ± 0.157	**< 0.001**		
Demographics					
Men, n (%)	44 (40)	47 (48)	0.24		
Age, yrs	50 ± 13	57 ± 9	**< 0.001**		
BMI, kg/m^2	27.7 ± 6.8	27.9 ± 6.6	0.89		
Waist circumference, cm	94 ± 15	94 ± 20	0.91		
Systolic pressure, mmHg	137 ± 22	136 ± 19	0.74		
Diastolic pressure, mmHg	79 ± 13	80 ± 11	0.63		
Comorbidity, n (%)					
Hypertension	24 (22)	52 (54)	**< 0.001**		
Dyslipidemia	64 (59)	50 (52)	0.15		
Current smoking	30 (28)	28 (29)	0.83		
Diabetes	7 (6)	14 (14)	0.058		
BMI > 30	15 (14)	27 (28)	**0.011**		
Statins	32 (29)	80 (82)	**< 0.001**		
Laboratory data					
ESR, mm/h	7 (4–13)	5 (3–11)	0.94		
hsCRP, mg/l	0.3 (0.1–0.8)	0.2 (0.1–0.7)	0.19		
Cholesterol, mg/dl	197 ± 36	179 ± 40	**0.001**		
Triglycerides, mg/dl	96 ± 39	108 ± 62	0.10		
LDL-C, mg/dl	116 ± 35	106 ± 34	**0.032**		
HDL-C, mg/dl	58 ± 17	55 ± 17	0.32		
Atherogenic index	3.37 (2.73–4.12)	3.62 (2.89–4.41)	0.68		
PsA-related data					
Type of PsA					
Peripheral oligoarthritis	14 (13)	5 (5)	**0.001**		
Peripheral polyarthritis	55 (50)	69 (71)			
Spondylitis	15 (14)	15 (15)			
Mixed	24 (22)	6 (6)			
Disease duration, yrs	4.1 (1.4–8.0)	5.7 (2.2–12.5)	**0.023**	1.00 (0.97–1.02)	0.77
Psoriasis at the time of the study, n (%)	76 (70)	75 (77)	0.093	1.66 (0.65–4.25)	0.30
HLA-B27–positive, n (%)	17 (16)	3 (3)	**0.004**	0.17 (0.03–1.06)	0.058
Positive family history of PsA, n (%)	40 (37)	29 (30)	0.23	0.76 (0.29–1.96)	0.56
BASDAI, total score	2.65 (0.00–5.70)	1.4 (0.0-3.8)	0.21	0.92 (0.74–1.13)	0.41
BASDAI > 4, n (%)	19 (17)	12 (12)	0.19	0.54 (0.16-1.84)	0.33
BASFI, total score	0.3 (0.0–3.5)	0.0 (0.0–2.1)	0.40	0.88 (0.70–1.11)	0.27
PsAID, total score	1.0 (0.0–3.2)	1.0 (0.0–2.0)	0.11	1.03 (0.77–1.37)	0.87
DAPSA, total score	1.92 (0.00–10.01)	6.10 (0.05–15.10)	0.056	**1.10 (1.02–1.19)**	**0.019**
Remission, n (%)	35 (32)	23 (24)	**0.049**	—	—
Low, moderate, or high activity, n (%)	23 (21)	32 (33)		**3.22 (1.05–9.90)**	**0.041**
DAPSA, total score, n (%)					
Remission	35 (32)	23 (24)	0.14	—	—
Low activity	13 (12)	17 (18)		1.50 (0.42–5.37)	0.53
Moderate or high activity	10 (9)	15 (15)		**15.09 (1.69–135.08)**	**0.015**
BSA, total score	0.5 (0.0–2.9)	0.9 (0.0–2.0)	0.30	0.79 (0.52–1.22)	0.29
PASI, total score	0.8 (0.0–2.1)	0.2 (0.0–2.0)	0.30	0.73 (0.51–1.04)	0.73
Low	42 (39)	44 (45)	0.27	—	—
Moderate and severe	6 (6)	2 (2)		0.10 (0.01–1.48)	0.094
NAPSI, total score	0 (0–3)	0 (0–4)	0.43	1.08 (0.93–1.26)	0.45
Log PGA, total score	0.37 ± 0.88	0.42 ± 0.64	0.82	1.80 (0.57–5.70)	0.32
Axial symptoms, n (%)	44 (40)	26 (13)	**0.046**	0.86 (0.36–2.07)	0.74
Peripheral symptoms, n (%)	83 (76)	67 (33)	0.31	0.57 (0.22–7.85)	0.23
Hip symptoms, n (%)	29 (27)	15 (7)	0.053	0.38 (0.14–1.07)	0.067
Enthesitis, n (%)	47 (43)	31 (15)	0.14	0.93 (0.39–2.14)	0.87
Uveitis, n (%)	8 (7)	5 (2)	0.54	0.75 (0.17–3.39)	0.75
Dactylitis, n (%)	28 (26)	23 (11)	0.79	1.30 (0.47–3.58)	0.61
Inflammatory bowel disease, n (%)	8 (7)	6 (3)	0.80	0.63 (0.15–2.60)	0.63

Table 3. Continued.

	Reclassification into Very High Risk after Carotid Ultrasound			Adjusted Model*	
	No, n = 109	Yes, n = 97	p	OR (95% CI)	p
Sacroiliitis on MRI, n (%)	17 (16)	9 (4)	0.21	0.74 (0.21–2.61)	0.64
Sacroiliitis in radiograph grade				0.69 (0.20–2.39)	0.69
Grade I, n (%)	55 (50)	47 (48)	0.62	—	—
Grade ≥ II, n (%)	16 (15)	11 11)		0.72 (0.21–2.51)	0.60
Syndesmophytes in axial radiograph, n (%)	4 (4)	3 (3)	0.99	0.52 (0.08–3.34)	0.49
Current NSAID, n (%)	91 (83)	71 (73)	0.12	0.45 (0.17–1.20)	0.11
Current prednisone, n (%)	44 (40)	41 (42)	0.59	1.02 (0.45–6.74)	0.96
DMARD, n (%)	78 (72)	76 (37)	0.11	2.32 (0.87–6.24)	0.095
Methotrexate, n (%)	71 (65)	68 (70)	0.30	1.25 (0.52–3.03)	0.62
Anti-TNF therapy, n (%)	50 (46)	37 (38)	0.32	1.41 (0.57–3.52)	0.63

* Adjusted model for age, hypertension, dyslipidemia, diabetes, obesity, and statins. Data represent mean ± SD or median (IQR) when data were not normally distributed. Values in bold face are statistically significant. PsA: psoriatic arthritis; cIMT: carotid intima-media thickness; BMI: body mass index; ESR: erythrocyte sedimentation rate; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; BASDAI: Bath Ankylosing Spondylitis Disease Activity; BASFI: Bath Ankylosing Spondylitis Functional Index; DAPSA: Disease Activity for PSoriatic Arthritis; PsAID: PsA Impact of Disease Score; BSA: body surface area; PASI: Psoriasis Area and Severity Index; NAPSI: Nail Psoriasis Severity Index; PGA: Psoriasis Global Assessment; MRI: magnetic resonance imaging; NSAID: nonsteroidal antiinflammatory drug; DMARD: disease-modifying antirheumatic drug; TNF: tumor necrosis factor; IQR: interquartile range.

Table 4. All the logistic regression model subsets for the prediction of reclassification in patients with PsA included in the low and moderate cardiovascular risk category according to the SCORE prior to carotid ultrasound assessment.

Variables	OR (95% CI)	p	Optimal Cutoff	Sensitivity, %	Specificity, %
Age, yrs	1.12 (1.03–1.21)	**0.006**	48	81	59
Statin treatment	90 (14–573)	**< 0.001**			
DAPSA	1.13 (1.02–1.25)	**0.024**	5	60	63
Pseudo R^2	0.562				
AIC	53				
SBIC	62				
AUC	0.932				
Sensitivity, %	93.8				
Specificity, %	84.6				
pfitHL	0.996				

Values in bold face are statistically significant. PsA: psoriatic arthritis; SCORE: Systematic Coronary Risk Evaluation; DAPSA: Disease Activity for Psoriatic Arthritis; AIC: Akaike information criterion; SBIC: Schwarz Bayesian information criterion; AUC: area under the curve; pfitHL: Hosmer-Lemeshow goodness-of-fit.

following carotid US evaluation[30]. Subclinical atherosclerosis was associated with age and dyslipidemia, but not with other traditional CV risk factors. Axial disease was associated with reclassification in patients with moderate CV risk[30]. Similarly, in a series of 226 patients with PsA, Eder, *et al* observed that 56.1% of the patients in the Framingham Risk Score–based low to intermediate risk groups had carotid plaques. Interestingly, 55.9% of the patients from the intermediate risk category were reclassified into an US-based high risk category, while 47.1% of the patients in the low risk category were reclassified into a higher US-based risk group[9].

The DAPSA score has been validated for its use in PsA. In both trials and observational studies, it has proven to be sensitive to change, showing good correlation with US-assessed synovitis[18]. Several reports have demonstrated that disease activity, as determined by this score or by other biomarkers, is responsible for the accelerated atherogenesis observed in patients with PsA[3,31,32]. Our findings, which support the contention that DAPSA is independently related to reclassification, reinforce the importance of disease activity and disease duration as key factors in the development of accelerated atherosclerosis in patients with PsA. A recent prospective study has shown that patients achieving minimal disease activity were associated with lower risk of subclinical atherosclerosis progression[33]. Further, when we established a predictive model on the probability of being reclassified, we found that the DAPSA score, when combined

Table 5. Discrimination, reclassification, and calibration assessment of SCORE versus model adding clinical data*.

	SCORE	SCORE + Clinical Data	p
Reclassification in patients with SCORE < 5%			
Discrimination			
AUC	0.716 (0.668–0.764)	**0.863 (0.789–0.936)**	**< 0.001**
Reclassification			
NRI	—	**0.65 (0.38–0.92)**	**< 0.001**
IDI	—	**0.46 (0.36–0.56)**	**< 0.001**
Calibration			
HL test	< 0.001		0.890

* PsA clinical data includes age, statin use, and DAPSA score. P values in AUC rows represent the comparison of the second model with the first one (SCORE model), which is considered the reference. NRI and IDI are expressed as their values (95% CI) and p value; NRI and IDI are compared using the SCORE model as the reference. Values in bold face are statistically significant. SCORE: Systematic Coronary Risk Evaluation; AUC: area under the curve; NRI: net reclassification index; IDI: integrated discrimination improvement; DAPSA: Disease Activity for Psoriatic Arthritis; HL: Hosmer-Lemeshow chi-square statistical test; PsA: psoriatic arthritis.

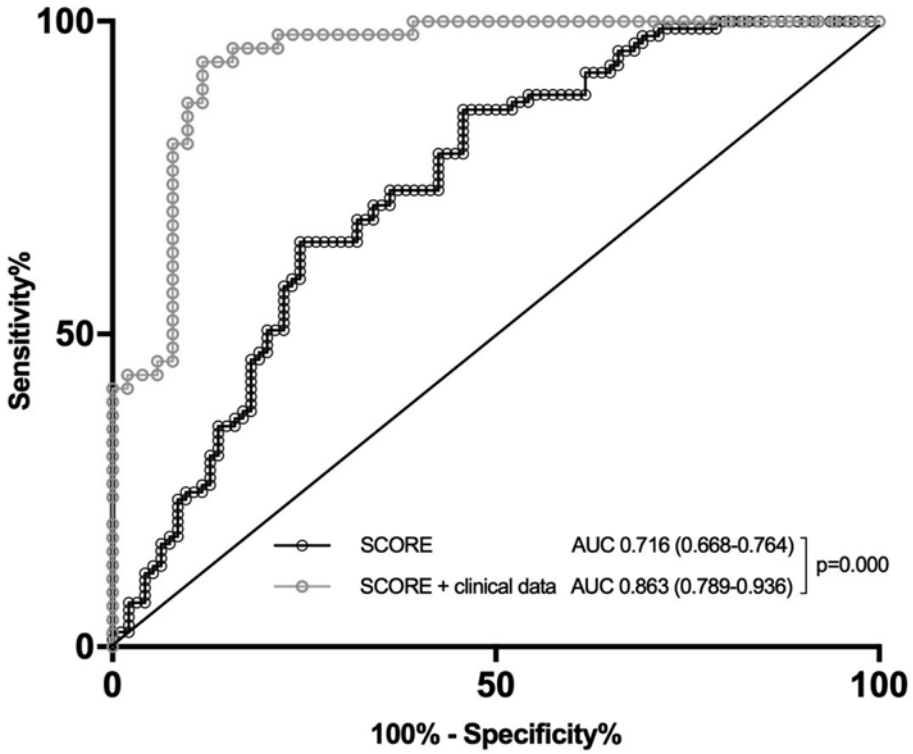

Figure 1. The receiver-operating characteristic (ROC) curves and the area under the ROC curve (AUC) for reclassification of both the SCORE model versus SCORE model plus clinical data (age, statin use, and DAPSA score). SCORE: Systematic Coronary Risk Evaluation; DAPSA: Disease Activity Index for Psoriatic Arthritis.

with age and statin treatment, was capable of explaining such a reclassification. Our findings were in agreement with a recent report by our group involving patients with SLE[10]. In that study, we found that disease-related factors, such as disease duration, a score of disease damage, and complement serum levels, were capable of explaining such a reclassification in patients with SLE, independently of traditional CV factors. These findings reinforce the pivotal role of disease activity in chronic inflammatory conditions as a major factor leading to CV risk reclassification.

We cannot explain exactly why other PsA disease-related scores were not related to reclassification. BASDAI index and cutaneous psoriasis scores did not reveal any differences between reclassified and non-reclassified patients. This was

probably related to a low prevalence of spinal involvement and mild skin involvement in our cohort. Moreover, the disease duration in our patients was relatively short. Because disease duration was short, it was not related to reclassification. In addition, the association of statin use with reclassification may reflect a marker of high underlying CV risk in these reclassified patients instead of a causative effect.

PsA may involve peripheral joints, axial joints, or both. However, polyarthritis is commonly observed during the disease course. Certainly, the polyarthritis pattern is the most common, and it is frequently associated with higher disease activity[34]. In our study, the peripheral polyarthritis PsA pattern was more commonly associated with reclassification than were other PsA patterns.

We found that both discrimination through AUC, which reflects the ability of a prognostic model to correctly identify clinical status, and reclassification with NRI were significantly higher in the model containing clinically related data compared to the SCORE model. The capacity of the SCORE model to predict clinical CV events in the general population is potent and has been widely demonstrated. In fact, improvements in risk prediction and classification beyond SCORE, such as by adding novel risk markers including imaging techniques and biomarkers, have been modest. In our study on patients with PsA, the contribution of SCORE data to a prediction model of reclassification was also great. However, we were able to identify novel markers (age, statin use, and DAPSA score) with a significant incremental predictive value for the presence of reclassification in PsA.

A limitation of our study was that controls were not age matched. However, this difference was not found to be excessive (mean difference of 4 yrs), and it is known that the SCORE model used age as a time variable and not as a risk factor. Moreover, it has previously been shown that regardless of matching, identical results are obtained when multivariable regression analysis is applied to epidemiological case-control studies[35]. Consequently, the multivariate analysis performed in our study was capable of dealing with potential confounders. In addition, patients in our cohort had significantly lower CRP serum levels compared to controls. This is perhaps because a large majority of the patients were receiving biological treatment. Nevertheless, this issue did not affect the results of our study. Another limitation was that currently it is unknown whether reclassified patients with PsA experience a higher number of CV events. Moreover, the reduction of CVD risk in patients treated with lipid- or blood pressure–lowering drugs because of reclassification with, for example, carotid US remains to be demonstrated. However, current guidelines[13] recommend additional risk factor assessment if such risk factors improve risk classification by calculation of NRI, and if the assessment is feasible in daily practice. This is the case of our study, in which NRI was proved to be statistically significant.

Our results indicate that reclassification of CV risk following carotid US assessment in patients with PsA is independently associated with disease activity. This fact supports the need for active management of the disease to reduce the inflammatory burden, in a dual strategy to prevent not only disability but also the risk of CV events.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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